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L6	L5 and (((micro or capillary or fluid) with channel) or microchannel or micro-channel)	2	L6
L5	L4 and (electric$6)	3	L5
L4	L2 and (capillary)	3	L4
L3	L2 and (electric$6 with signal)	1	L3
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L10: Entry 1 of 1 File: USPT Feb 27, 2001

US-PAT-NO: 6194900
DOCUMENT-IDENTIFIER: US 6194900 B1

TITLE: Integrated miniaturized device for processing and NMR detection of liquid phase samples

DATE-ISSUED: February 27, 2001

INVENTOR-INFORMATION:

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US-CL-CURRENT: 324/321; 324/318

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L10: Entry 1 of 1 File: USPT Feb 27, 2001

DOCUMENT-IDENTIFIER: US 6194900 B1
TITLE: Integrated miniaturized device for processing and NMR detection of liquid phase samples

US PATENT NO. (1):
6194900

Abstract Text (1):
A miniaturized total analysis system with an in-line NMR detection compartment and an NMR rf microcoil detector is described for use in liquid phase analysis. The device is formed by microfabrication of microstructures in novel support substrates. The NMR detector coil may be fabricated directly in the support body at the point of detection or, alternatively, may be formed as part of a modular structure that is insertable into the device at the point of detection. In addition, an integrated device for sample preparation and NMR detection is provided comprising the miniaturized total analysis system and a miniature magnet configured to accept the miniaturized total analysis system, wherein the device is capable of generating an NMR spectrum. The invention herein is used for the analysis of small and/or macromolecular and/or other solutes in the liquid phase.

Brief Summary Text (4):
Real time identification of analytes in a complex biological fluid is difficult, and requires careful thought as to (a) the preparation of the sample, (b) whether a separation step is required to simplify the signal, (c) whether a detection method can be employed which has no effect on the sample itself, (e.g. non-destructive). An ideal device would allow rapid detection of a wide range of simple or complex molecules in the liquid phase, at biological concentrations, and yield information about chemical structure and composition. A desirable feature of the detection method would be to enable the separation criteria to be relaxed such that sample preparation and detection could occur in series, without the need for complex separation technology. An on-line detector is particularly advantageous when sample size is limited, and additional analysis of the sample is required. Moreover, mass spectrometry ("MS") and NMR are detection methods well suited to yielding high quality chemical information for multi-component samples, requiring no a priori knowledge of the constituents.

Brief Summary Text (5):
Though much has been discussed in the literature towards realizing integrated separation technology including sample preparation and separation devices, and associated fluidics so that low yield or precious samples may be prepared and analyzed, little has been realized to date. In sample analysis instrumentation, particularly in separation systems involving capillary electrophoresis or liquid chromatography, smaller dimensions of the sample handling conduits and separation compartments result in improved performance characteristics, while reducing cost of production and analysis. Miniaturization of the sample preparation or separation region, to result in small sample volume requirements, necessarily means a greater demand on the detection method both by virtue of sample volume and potentially, sensitivity.

Brief Summary Text (7):
One of the most powerful analytical methods for molecular structure information is NMR. NMR provides spectral information as a function of the electronic environment of the molecule and is nondestructive to the sample. In addition, reaction rates, coupling constants, bond-lengths, and two- and three-dimensional structure can be

obtained with this technique. The strength of both NMR and MS is the ability to derive fundamental chemical structure information, which is high resolution in terms of either chemical shift or mass, yielding the possibility of simultaneous analysis of multiple species. The inherent insensitivity of the NMR method however, has limited its usefulness as a detection method for liquid phase analysis of very small samples, such as effluent from a liquid chromatography or capillary electrophoretic separation.

Brief Summary Text (8):
NMR combined with liquid chromatography or capillary electrophoresis was demonstrated as early as 1978 using stopped flow (Watanabe et al. (1978) Proc. Jpn. Acad. 54:194), and in 1979 with continuous flow (Bayer et al. (1979) J. Chromatog. 186:497-507), though limitations due to solvent as well as inherent sensitivity curtailed the use of the method. See Dorn et al. (1984) Anal. Chem. 56:747-758 for a review.

Brief Summary Text (10):
A number of areas can be targeted to increase the sensitivity of NMR detection for liquid phase analysis. Resistive losses, operating temperature, sample ionic strength, filling factor, and coil geometry affect the sensitivity of the coil. Cooling the radiofrequency coil and using superconducting coil material have resulted in some gain in signal-to-noise through reduction in coil resistance and thermal properties. However, it is difficult to achieve the theoretical maximum, since detecting signal from a room temperature liquid sample using a cryogenically cooled radiofrequency probe has proven difficult.

Brief Summary Text (11):
The NMR signal-to-noise is directly proportional to the sample volume (V.sub.s) interrogated by the detection coil (filling factor), the magnetization per unit volume (M.sub.o), and the strength of the radiofrequency ("RF") field (B.sub.1) per unit current, and inversely proportional to the square root of the coil resistance (R):

Brief Summary Text (12):
Signal-to-noise can be maximized by decreasing the coil radius, and matching the coil inner diameter as close to the size of the sample as possible. Inadequate filling factor will generally be an issue when standard radiofrequency NMR coils are used to detect signal from very small sample volumes, e.g., from a microcolumn or other miniaturized sample preparation technology. Reduction in the size of NMR radiofrequency coils to the diameter of the fused glass capillary used for these types of separations, has allowed detection of signal from nanoliter volumes from on-line capillary electrophoretic separations Wu et al. (1994a), supra; Olson et al. (1995), supra; Wu et al. (1994b), supra; Wu et al. (1995), supra.

Brief Summary Text (13):
A solenoid microcoil detection cell formed from a fused silica capillary wrapped with copper wire has been used for static measurements of sucrose, arginine and other simple compounds. Wu et al. (1994a), supra; Olson et al. (1995), supra. Coil diameter has been further reduced by the use of conventional micro-electronic techniques in which planar gold or aluminum R.F. coils having a diameter ranging from 10-200 .mu.m were etched in silicon dioxide using standard photolithography. Peck (1995) J. Magn. Reson. 108(B) 114-124. The signal-to-noise ratio (SNR) of these planar micro-coils for analyzing solid samples, e.g., silicon rubber was increased by a factor of 10 over other coils. For significant advancement in hyphenating NMR with LC or CE methods, an approach allowing micromolar or even nanomolar limits of detection is required however.

Brief Summary Text (14):
Factors affecting the limit of detection can also be attributed to bulk susceptibility shifts, which become dominant when the sample volume is of the order of the size of the sample chamber and coil. This is in addition to the coil geometry, resistive losses, sample ionic strength, filling factor and operating temperature considerations previously mentioned. We have constructed susceptibility-matched microcoils using 50 .mu.m copper wire with an inner diameter of 70 .mu.m, and obtained signal in 64 seconds from a 12.5 mM solution of arginine at 400 MHZ, with a signal-to-noise of 6:1. Or, in other words, normalizing these results to 300 MHZ for direct comparison with U.S. Pat. No. 5,654,636, issued Aug. 5, 1997, to Sweedler et al. this yields a signal-to-noise of 3:1 versus 1:1 obtained in Sweedler et al.

Brief Summary Text (15):
In order to obtain signal from nanoliter-volume samples having analyte in the micromolar concentration range, assuming limitations only of currently available field strength (750 MHZ) and a time constraint of observing signal after one minute of acquisition time from 5.4 nl of volume, the following parameters could be optimized: (a) reduce the wall thickness while keeping the sample volume the same increasing the filling factor; (b) increase the "Q" or quality factor of the coil by using a superconducting coil; and/or (c) employ sensitivity enhancement techniques such as decoupling or Nuclear Overhauser Enhancement (NOE), or optical pumping (with .sup.3 He). The following table provides a comparison of the limitation-of-detection before and after implementation of the above mentioned factors. The numbers below were obtained by converting the theoretical S/N advantage obtained by each method to time saved using the method. One minute was deemed acceptable; 1 hour is shown for comparison purposes.

Brief Summary Text (18):
A method and an apparatus for NMR spectroscopy of samples from online separation methods has been described. Sweedler et al., supra. While the problems of susceptibility and signal-to-noise from samples of an online separation apparatus are addressed therein, the method and apparatus described is limited to analysis of simple aqueous solutions. The apparatus includes a capillary channel etched or grooved in a substrate such as glass or polycarbonate and a planar lithographic microcoil. The use of micron-feature devices with integrated sample preparation and detection is not described. Integration of the NMR coil with the separation device eliminates dead volume which increases the dispersion and drastically degrades resolution between the point of chemical separation and detection. The method and apparatus presented in Sweedler et al. uses a conventional NMR spectrometer, such that sample preparation occurs outside of the separation/detection system, and hence a truly integrated solution for sample preparation and detection is lacking.

Brief Summary Text (22):
Accordingly, it is a primary object of the invention to provide a novel miniaturized separation system with an integrated NMR detection chamber and an NMR rf microcoil detector for on-line NMR analysis of samples separated.

Brief Summary Text (26):
The present invention is directed to a novel miniaturized total analysis system for liquid phase sample preparation and detection. The system comprises an NMR detection compartment and an NMR rf microcoil detector.

Brief Summary Text (27):
The inventors are not aware of any integrated miniaturized system comprising sample processing including sample pretreatment, separation and NMR detection integrated with an NMR rf microcoil for liquid phase analysis. Accordingly, the invention, as now provided, represents a novel and important advance in liquid phase analysis using miniaturized devices. It has been found by the inventors that the integration of an NMR rf microcoil detector with the processing device as now provided eliminates dead volume between the point of chemical preparation and processing and point of detection, and thereby obviates a common source of artifact and signal acquisition delay encountered with stand-alone processing devices interfaced with an NMR instrument. In addition, on-line analysis with the NMR rf microcoil detector enables a faster time-to-result and analysis with increased sensitivity of detection.

Brief Summary Text (29):
a microfabricated support body having first and second substantially planar opposing surfaces wherein the support body has a microchannel microfabricated in the first planar surface;

Brief Summary Text (30):
a cover plate arranged over the first planar surface, wherein the cover plate in combination with the first microchannel forms a sample processing compartment;

Brief Summary Text (32):
downstream from the sample processing compartment and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil.

Brief Summary Text (35):

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

Brief Summary Text (36):
an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

Brief Summary Text (38):
downstream from the elongate bore and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil. The NMR detection compartment and the NMR rf microcoil may be fabricated directly in the support body at the point of detection. Alternatively, the NMR detection compartment and the NMR rf microcoil are formed in an insertable modular structure.

Brief Summary Text (41):
The system comprises microchannels and chambers for sample preparation, separation and detection. For example, a biological sample such as blood, urine, milk, cell or tissue extract, fermentation product or the like is added directly to the planar device. The sample is then prepared as required for the particular separation process to be performed, i.e., filtration, solid phase extraction, capillary electrophoresis or liquid chromatography. The prepared sample is then shunted to a separation chamber, and immediately following separation, detected in an NMR detection chamber. The NMR detection chamber has an integrated NMR radiofrequency coil embedded directly in the support media. Following detection, the sample can be discarded or, optionally, transported on chip to a further analytical station. The total analysis would require less than 1 .mu.L of sample.

Brief Summary Text (42):
The integrated system therefore, provides on-device sample preparation, separation and detection, as well as a transport medium for further analysis if required, an important feature when sample volumes of less than 1 .mu.L are to be handled. The miniaturized separation device can be formed from a polymer support body having essentially planar halves with microchannels and apertures fabricated therein. When aligned, the two halves define a separation compartment having inlet and outlet ports, an NMR detection chamber and an NMR radiofrequency coil.

Brief Summary Text (43):
In yet another embodiment, an integrated device for sample preparation and NMR detection is provided. The device comprises the aforementioned miniaturized total analysis system and a magnet configured to accept the a miniaturized total analysis system, wherein the device is capable of generating an NMR spectrum. The integrated device with NMR micro-coil is positioned within the center of the homogeneous field of the magnet, which is comprised of: (1) a miniature, e.g., table-top, magnet, such as is currently manufactured by American Magnetics Corp, of field strength of at least 300 MHZ to 750 MHZ; (2) associated electronics and data acquisition and storage capabilities for acquisition of, display and storage of multinuclear NMR spectra acquired from the rf microcoil; and (3) appropriate shielding of the NMR magnet so that the ensemble, i.e., the liquid phase analysis device, the NMR micromagnet and associated peripherals, can be situated easily on a table top or counter.

Drawing Description Text (9):
FIG. 7A (prior art) is an exploded view of a first side of a miniaturized column device having microchannels formed on two opposing planar surfaces of a support substrate.

Drawing Description Text (30):
FIG. 24 is a pictorial representation of a miniaturized total analysis system with an NMR detection compartment and an NMR rf microcoil. FIG. 24A illustrates a miniaturized total analysis system in which the NMR detection compartment and the NMR rf microcoil are fabricated in the support body. FIG. 24B illustrates a miniaturized total analysis system in which the NMR detection compartment and the NMR rf microcoil are components of a modular structure removably insertable into the support body. In addition, FIG. 24A schematically illustrates a separation device with on-board transmit-receive circuitry, while FIG. 24B illustrates the device with on-board receive-only circuitry.

Detailed Description Text (2):
Before the invention is described in detail, it is to be understood that this invention is not limited to the particular component parts of the devices described or process steps of the methods described as such devices and methods may vary. It is also to be understood that the terminology used herein is for purposes of describing particular embodiments only, and is not intended to be limiting. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an analyte" includes mixtures of analytes, reference to "a detection means" includes two or more such detection means, reference to "a sample processing compartment" includes more than one such compartment, reference to "an NMR rf microcoil" includes two or more such microcoils, and the like.

Detailed Description Text (8):
The term "sample handling region" refers to a portion of a microchannel, or to a portion of a "sample processing compartment" that is formed upon enclosure of the microchannel by a cover plate or substrate in which a mirror image of the microchannel has been microfabricated as described below, that includes a "sample flow component" or a "sample treatment component." By the term "sample flow component" is intended a portion of the sample processing compartment that interconnects sample treatment components.

Detailed Description Text (11):
As used herein, the term "NMR rf detector" or "NMR detection means" refers to any means, structure or configuration which allows one to interrogate a sample within an on-device NMR microcoil using an external magnet. Thus, an NMR detection means an NMR microcoil that communicates with the sample processing compartment and allows an external magnet to be interfaced with the sample processing compartment to detect an analyte passing through the compartment.

Detailed Description Text (13):
As used herein, a "lightguide means" refers to a substantially long, thin thread of a transparent substance which can be used to transmit light. Lightguide means useful in the practice of the invention include optical fibers, integrated lens configurations and the like. In particularly preferred embodiments, optical fibers are interfaced with detection means to enable optical detection techniques known in the art. The terms "optical fiber," "fiber optic waveguide" or "optical fiber means" are used herein to refer to a single optical fiber or a bundle optical fibers, optionally encased in a protective cladding material. Examples of suitable optical fiber substrate materials include glass, plastic, glass/glass composite and glass/plastic composite fibers. A critical characteristic of optical fibers is attenuation of an optical signal. Further, a chemical sensor can be incorporated into a fiber optic waveguide in a manner such that the chemical sensor will interact with the liquid sample analyte. Structures, properties, functions and operational details of such fiber optic chemical sensors can be found in U.S. Pat. No. 4,577,109 to Hirschfeld, U.S. Pat. No. 4,785,814 to Kane, and U.S. Pat. No. 4,842,783 to Blaylock.

Detailed Description Text (14):
The use of microfabrication techniques such as, but not limited to, laser ablation, molding and embossing, in the practice of the invention allows for a high degree of precision in the alignment of micro-scale components and structures, which alignment has either been difficult or not possible in prior substrate-based devices. Thus, the term "microalignment" as used herein refers to the precise and accurate alignment of microfabricated features, including the enhanced alignment of complementary microchannels or microcompartments with each other, inlet and/or outlet ports with microchannels or separation compartments, detection means with microchannels or separation compartments, detection means with other detection means, and the like.

Detailed Description Text (15):
The term "microalignment means" is defined herein to refer to any means for ensuring the precise microalignment of microfabricated features in a miniaturized column device. Microalignment means can be formed in the column devices either by laser ablation or by other methods of fabricating shaped pieces well known in the art. Representative microalignment means that can be employed herein include a plurality of co-axially arranged apertures microfabricated in component parts and/or a

plurality of corresponding features in column device substrates, e.g., projections and mating depressions, grooves and mating ridges or the like. Alternative alignment means includes features forms in component parts such as pin and mating aperture. Further, the accurate microalignment of component parts can be effected by forming the miniaturized columns in flexible substrates having at least one fold means microfabricated therein, such that sections of the substrate can be folded to overlie other sections thereby forming composite micro-scale compartments, aligning features such as apertures or detection means with separation compartments, or forming micro-scale separation compartments from microchannels. Such fold means can be embodied by a row of spaced-apart perforations fabricated in a particular substrate, a contiguous slot-like depression or a series spaced-apart slot-like depressions or apertures microfabricated in the substrate so as to extend only part way therethrough, or the like. The perforations or depressions can have circular, diamond, hexagonal or other shapes that promote hinge formation along a predetermined straight line.

Detailed Description Text (18):
"Electrophoretic" separations refers to the migration of particles or macromolecules having a net electric charge where said migration is influenced by an electric field. Accordingly electrophoretic separations contemplated for use in the invention include separations performed in columns packed with gels (such as poly-acrylamide, agarose and combinations thereof) as well as separations performed in solution.

Detailed Description Text (20):
The term "motive force" is used to refer to any means for inducing movement of a sample along a column in a liquid phase analysis, and includes application of an electric potential across any portion of the column, application of a pressure differential across any portion of the column or any combination thereof.

Detailed Description Text (21):
The term "surface treatment" is used to refer to preparation or modification of the surface of a microchannel which will be in contact with a sample during separation, whereby the separation characteristics of the device are altered or otherwise enhanced. Accordingly, "surface treatment" as used herein includes: physical surface adsorptions; covalent bonding of selected moieties to functional groups on the surface of microchannel substrates (such as to amine, hydroxyl or carboxylic acid groups on condensation polymers); methods of coating surfaces, including dynamic deactivation of channel surfaces (such as by adding surfactants to media), polymer grafting to the surface of channel substrates (such as polystyrene or divinyl-benzene), sputter deposition of metallic materials and thin-film deposition of materials such as diamond or sapphire to microchannel substrates.

Detailed Description Text (30):
The term "LIGA process" is used to refer to a process for fabricating microstructures having high aspect ratios and increased structural precision using synchrotron radiation lithography, galvanoforming, and plastic molding. In a LIGA process, radiation sensitive plastics are lithographically irradiated at high energy radiation using a synchrotron source to create desired microstructures (such as channels, ports, apertures and micro-alignment means), thereby forming a primary template.

Detailed Description Text (34):
The term "NMR rf microcoil" is used herein to refer to an NMR rf coil having a cross-sectional area less than 1 mm.sup.2.

Detailed Description Text (37):
The term "coil filling factor" refers to the ratio of the inner diameter of the capillary to the diameter of the coil surrounding it. The coil filling factor reflects the number of nuclei per unit volume that can be interrogated by the radiofrequency pulse. The signal is proportional to the number of resonant nuclei per unit volume, hence for a given coil diameter, a thinner walled chamber will allow more nuclei to be interrogated than in a thick walled chamber.

Detailed Description Text (38):
The term "multiple receive coils" refers to two or more receive coils, mutually decoupled, each feeding a separate receive chain, with signal summed after reception.

Detailed Description Text (46):

In a preferred embodiment of the invention, channels of a semi-circular cross section are laser ablated by controlling exposure intensity or by making multiple exposures with the beam being reoriented between each exposure. Accordingly, when a corresponding semi-circular channel is aligned with a channel thus formed, a sample processing chamber of highly symmetrical circular cross-section is defined which may be desirable for enhanced fluid flow through the sample processing device.

Detailed Description Text (51):
Referring now to FIGS. 1-3, the substrate 4 has a microchannel 10 laser-ablated in a first planar surface 6. It will be readily appreciated that, although the microchannel 10 has been represented in a generally extended form, microchannels formed according to the invention may be ablated in a large variety of configurations, such as in a straight, serpentine, spiral, or any tortuous path desired. Further, as described in greater detail above, the microchannel 10 may be formed in a wide variety of channel geometries including semi-circular, rectangular, rhomboid, and the like, and the channels may be formed in a wide range of aspect ratios. It is also noted that a device having a plurality of microchannels laser-ablated thereon falls within the spirit of the present invention.

Detailed Description Text (52):
Referring particularly to FIGS. 1 and 4, a cover plate 12 is arranged over said first planar surface 6 and, in combination with the laser-ablated microchannel 10, forms an elongate sample processing compartment 14. Cover plate 12 may be formed from any suitable substrate such as polyimide, the selection of the substrate only being limited by avoidance of undesirable separation surfaces such as silicon or silicon dioxide materials.

Detailed Description Text (56):
It is noted that the ablated by-pass channel 24 and apertures 26 and 28 further enable a wide variety of sample introduction techniques to be practiced according to the invention. Particularly, having a by-pass channel which is not connected to the sample processing compartment allows a user to flush a sample through the by-pass channel without experiencing sample carry-over or column contamination. As will be appreciated by one of ordinary skill in the art after reading this specification, one such sample introduction technique may be effected by butt-coupling an associated rotor to a stator (not shown) on the external surface of a miniaturized column where the rotor selectively interfaces external tubing and fluid sources with inlet port 18 and apertures 26 and 28, allowing a sample to be flushed from the by-pass channel 24 into external tubing from which the sample may then be introduced into the column via inlet port 18 for liquid phase analysis thereof. In this regard, a miniaturized column device formed in a polyimide substrate enables a ceramic rotor, pressed to the device using tensioned force (to form a liquid-tight seal), to still rotate between selected aperture positions on the device due to the friction characteristics of the two materials. Other suitable rotors can be formed in rigid materials such as, but not limited to, glass and non-conductive substrates.

Detailed Description Text (58):
Also according to the invention, a wide variety of means for applying a motive force along the length of the sample processing compartment 14 may be associated with the subject device. In this regard, a pressure differential or electric potential may be applied along the entire length of the sample processing compartment by interfacing motive means with inlet port 18 and outlet port 22.

Detailed Description Text (61):
Referring to FIG. 5, a further embodiment of the invention, indicated at 2' is shown comprising a preferred detection means indicated generally at 42. More particularly, a first transparent sheet 38 is provided wherein the cover plate 12 is interposed between said first transparent sheet and substrate 4. A second transparent sheet 40 is also provided wherein the second sheet is disposed over the second planar surface 8 of the substrate 4. In this manner, detection means 42 allows optical detection of separated analytes passing through sample processing compartment, formed by the combination of microchannel 10 and cover plate 12, via transmission of radiation orthogonal to the major axis of the sample processing compartment (and, accordingly, orthogonal to the direction of electro-osmotic flow in an electrophoretic separation). Further, in the practice of the invention, the transparent sheets may comprise materials such as quartz, diamond, sapphire, fused silica or any other suitable substrate which enables light transmission therethrough.

Detailed Description Text (67):

Accordingly, in the present invention wherein detection path lengths exceeding 250 .mu.m are desired, an alternative device embodiment is provided having laser-ablated features on two opposing surfaces of a substrate. More particularly, in FIGS. 7A and 7B, a further embodiment of a miniaturized column device is generally indicated at 52. The miniaturized column comprises a substrate 54 having first and second substantially planar opposing surfaces respectively indicated at 56 and 58. The substrate 54 has a first microchannel 60 laser ablated in the first planar surface 56 and a second microchannel 62 laser ablated in the second planar surface 58, wherein the microchannels can be provided in a wide variety of geometries, configurations and aspect ratios as described above.

Detailed Description Text (68):
The miniaturized column device of FIGS. 7A and 7B further includes first and second cover plates, indicated at 64 and 66 respectively, which, in combination with the first and second microchannels 60 and 62, define first and second elongate separation compartments when substrate 54 is sandwiched between the first and second cover plates.

Detailed Description Text (69):
Referring still to FIGS. 7A and 7B, a plurality of apertures can be laser-ablated in the device to provide an extended separation compartment, and further to establish fluid communication means. More particularly, a conduit means 72, comprising a laser ablated aperture in substrate 54 having an axis which is orthogonal to the first and second planar surfaces 56 and 58, communicates a distal end 74 of the first microchannel 60 with a first end 76 of the second microchannel 62 to form an extended separation compartment.

Detailed Description Text (70):
Further, an aperture 68, laser ablated in the first cover plate 64, enables fluid communication with the first microchannel 60, and a second aperture 70, laser ablated in the second cover plate 66, enables fluid communication with the second microchannel 62. As will be readily appreciated, when the aperture 68 is used as an inlet port, and the second aperture 70 is used as an outlet port, a miniaturized column device is provided having a flow path extending along the combined length of the first and second microchannels 60 and 62.

Detailed Description Text (76):
Thus, the miniaturized column device 52' is formed by laser ablating a first microchannel 60' in the first planar surface 56' of the column portion 88B, and a second microchannel 62' in the second planar surface 58' of the column portion. Each microchannel can be provided in a wide variety of geometries. configurations and aspect ratios. A first separation compartment is then formed by folding the flexible substrate 88 at the first fold means 90 such that the first cover plate portion 88A covers the first microchannel 60' to form an elongate separation compartment. A second separation compartment is then provided by folding the flexible substrate 88 at the second fold means 92 such that the second cover plate portion 88C covers the second microchannel 62' to form a separation compartment as described above. A conduit means 72', comprising a laser ablated aperture in the column portion 88B having an axis which is orthogonal to the first and second planar surfaces 56' and 58', communicates a distal end of the first microchannel 60' with a first end of the second microchannel 62' to form a single, extended separation compartment.

Detailed Description Text (77):
Further, an aperture 68', laser ablated in the first cover plate portion 88A, enables fluid communication with the first microchannel 60', and a second aperture 70', laser ablated in the second cover plate portion 88C, enables fluid communication with the second microchannel 62'. As described above, when the first and second apertures are used as an inlet and outlet port, respectively, a miniaturized column device is provided having a flow path extending along the combined length of the first and second microchannels.

Detailed Description Text (80):
Accordingly, novel miniaturized column devices have been described which are laser ablated into a substrate other than silicon or silicon dioxide materials, and which avoid several major problems which have come to be associated with prior attempts at providing micro-column devices. The use of laser ablation techniques in the practice of the invention enables highly symmetrical and accurately defined micro-column devices to be fabricated in a wide class of polymeric and ceramic substrates to provide a variety of miniaturized liquid-phase analysis systems. In this regard,

miniaturized columns may be provided which have micro-capillary dimensions (ranging from 5-200 .mu.m in diameter) and column detection path lengths of up to 1 mm or greater. This feature has not been attainable in prior attempts at miniaturization, such as in capillary electrophoresis, without substantial engineering of a device after capillary formation. Further, laser ablation of miniaturized columns in inert substrates such as polyimides avoids the problems encountered in prior devices formed in silicon or silicon dioxide-based materials. Such problems include the inherent chemical activity and pH instability of silicon and silicon dioxide-based substrates which limits the types of separations capable of being performed in those devices.

Detailed Description Text (82):
Laser ablation of microchannels in the surfaces of the above-described substrates has the added feature of enabling a wide variety of surface treatments to be applied to the microchannels before formation of the sample processing compartment. That is, the open configuration of laser-ablated microchannels produced using the method of the invention enables a number of surface treatments or modifications to be performed which are not possible in closed format constructions, such as in prior micro-capillaries. More specifically, laser ablation in condensation polymer substrates provides microchannels with surfaces featuring functional groups, such as carboxyl groups, hydroxyl groups and amine groups, thereby enabling chemical bonding of selected species to the surface of the subject microchannels using techniques well known in the art. Other surface treatments enabled by the open configuration of the instant devices include surface adsorptions, polymer graftings and thin film deposition of materials such as diamond or sapphire to microchannel surfaces using masking and deposition techniques and dynamic deactivation techniques well known in the art of liquid separations.

Detailed Description Text (85):
The first and second component halves 106 and 108 each have substantially planar interior surfaces, indicated at 110 and 112 respectively, wherein miniaturized column features may be laser ablated. More particularly, a first microchannel pattern 114 is laser ablated in the first planar interior surface 110 and a second microchannel pattern 116 is laser ablated in the second planar interior surface 112. According to the invention, said first and second microchannel patterns are ablated in the support body 104 so as to provide the mirror image of each other.

Detailed Description Text (86):
Referring now to FIGS. 11 and 12, a sample processing compartment 118, comprising an elongate bore defined by the first and second microchannel patterns 114 and 116 may be formed by aligning (such as by folding) the first and second component halves 106 and 108 in facing abutment with each other. In the practice of the invention, the first and second component halves may be held in fixable alignment with one another to form a liquid-tight sample processing compartment using pressure sealing techniques, such as by application of tensioned force, or by use of adhesives well known in the art of liquid phase separation devices. It is further contemplated according to the invention to form first and second microchannels 114 and 116 having semi-circular cross-sections whereby alignment of the component halves defines a sample processing compartment 118 having a highly symmetrical circular cross-section to enable enhanced fluid flow therethrough; however, as discussed above, a wide variety of microchannel geometries are also within the spirit of the invention.

Detailed Description Text (87):
In a further preferred embodiment of the invention, it is particularly contemplated to form the support body 104 from a polymer laminate substrate comprising a Kapton.RTM. film co-extruded with a thin layer of a thermal plastic form of polyimide referred to as KJ.RTM. and available from DuPont (Wilmington, Del.). In this manner, the first and second component halves 106 and 108 may be heat sealed together, resulting in a liquid-tight weld that has the same chemical properties and, accordingly, the same mechanical, electrical and chemical stability, as the bulk Kapton.RTM. material.

Detailed Description Text (88):
Referring now to FIGS. 10-12, the miniaturized column device 102 further comprises means for communicating associated external fluid containment means (not shown) with the sample processing compartment 118 to provide a liquid-phase separation device. More particularly, a plurality of apertures may be laser ablated in the support body 104, wherein said apertures extend from at least one exterior surface of the support body and communicate with at least one microchannel, said apertures permitting the

passage of fluid therethrough. In this regard, an inlet port 120 may be laser ablated in the first component half 106 and communicate with a first end 122 of said first microchannel 114. In the same manner, an outlet port 124 may be ablated in the first component half and communicate with a second end 126 of said first microchannel 114.

Detailed Description Text (89):
As is readily apparent, a liquid phase sample processing device may thereby be formed, having a flow path extending from the first end 122 of the microchannel 114 to the second end 126 thereof, by communicating fluids from an associated source (not shown) through the inlet port 120, passing the fluids through the sample processing compartment 118 formed by the alignment of microchannels 114 and 116, and allowing the fluids to exit the sample processing compartment via the outlet port 126. In this manner, a wide variety of liquid phase analysis procedures may be carried out in the subject miniaturized column device using techniques well known in the art. Furthermore, various means for applying a motive force along the length of the sample processing compartment 118, such as a pressure differential or electric potential, may be readily interfaced to the column device via the inlet and outlet ports, or by interfacing with the sample processing compartment via additional apertures which may be ablated in the support body 104.

Detailed Description Text (91):
Referring now to FIGS. 10 and 11, the miniaturized column device 102 further comprises detection means laser ablated in the support body 104. More particularly, a first aperture 128 is ablated in said first component half 106 and communicates with the first microchannel 114 at a point near the second end 126 thereof. A second aperture 130 is likewise formed in said second component half 108 to communicate with the second microchannel 116. Accordingly, a wide variety of associated detection means, e.g., NMR detection means, may then be interfaced to the sample processing compartment 118 to detect separated analytes of interest passing therethrough, such as by connection of electrodes to the miniaturized column via the first and second apertures 128 and 130.

Detailed Description Text (93):
Accordingly, there have been described several preferred embodiments of a miniaturized column device formed according to the invention by laser ablating microstructures on component parts and aligning the components to form columns having enhanced symmetries. As described in detail above, formation of the subject microchannels in the open configuration enables a wide variety of surface treatments and modifications to be applied to the interior surfaces of the channels before formation of the sample processing compartment. In this manner, a wide variety of liquid phase analysis techniques may be carried out in the composite sample processing compartments thus formed, including chromatographic, electrophoretic and electrochromatographic separations.

Detailed Description Text (94):
In the practice of the invention, it is further contemplated to provide optional means for the precise alignment of component support body halves, thereby ensuring accurate definition of a composite sample processing compartment formed according to the invention. More particularly, in a further preferred embodiment of the invention, micro-alignment means are provided to enable enhanced alignment of laser-ablated component parts such as microchannels, detection apertures and the like.

Detailed Description Text (103):
The manifold 194 can be coupled to the cover plate 196 to form a liquid-tight interface using pressure sealing techniques known in the art. The manifold and cover plate can be mechanically urged together using clips, tension springs or any suitable clamping means known in the art. The manifold 194 generally includes a plurality of ports that are configured to correspond with the pattern of apertures and inlets present in the cover plate 196. Referring particularly to FIG. 16, a first conduit 204 can be used to interface an associated containment means (not shown) housing a sample to be separated, or a suitable buffer, with the separation channel 206. The conduit 204 is interposed within a port 208 in the manifold 194, and arranged to be in fluid communication with the upstream terminus 210 of the separation channel 206 via the inlet port 200. In this manner, fluids from the associated containment means can be readily delivered to the separation compartment using known injection methods.

Detailed Description Text (104):
The liquid phase separation apparatus 190 can include a column 198 having an optional bypass microchannel 212 laser-ablated in the substrate 214, whereby a volumetric sample compartment is formed in combination with the cover plate 196. The bypass microchannel has first and second termini, 216 and 218, which respectively cooperate with first and second laser-ablated apertures 220 and 222 that are arranged in the cover plate 196 to correspond with the subject termini when the cover plate is aligned over the substrate 214.

Detailed Description Text (105):
Second and third conduit means, 224 and 226, are respectively interposed within ports 228 and 230 in the manifold 194, whereby the conduit means communicate with the bypass microchannel 212 at the first and second termini, 216 and 218, via the first and second laser-ablated apertures 220 and 222. A sample plug having the dimensions of the volumetric sample compartment is thus provided by passing sample through the compartment from an associated containment means using the conduits 224 and 226 to provide a sample flow path to and from the containment means. By manually removing conduits 204, 224 and 226 from the manifold 194, and coupling manifold ports 228 and 208 together by way of a single conduit, a new flow path is provided that passes from the volumetric sample compartment to the upstream terminus 210 of the separation compartment. By coupling the manifold port 230 with a further conduit means that is in fluid communication with a second associated containment means housing a suitable liquid medium, the sample plug can be flushed from the volumetric sample compartment and delivered into the separation compartment by conveying medium from the second containment means to the manifold using known fluid injection methods.

Detailed Description Text (106):
Once the sample has been delivered to the separation compartment, various means for applying a motive force along the length of the separation compartment can be interfaced to the column device 304 using the manifold 306. Particularly, a pressure differential or electric potential can be established along the length of the separation compartment by coupling an external motive means to the upstream terminus of the separation channel via a manifold port.

Detailed Description Text (109):
The column device 304 also includes a makeup flow channel 320 laser-ablated in the planar surface 312. A makeup flow compartment is formed by the combination of the cover plate 316 and the makeup flow microchannel 320. The makeup flow channel has an upstream terminus, 322, which is in fluid communication with a makeup inlet port 324, comprising an aperture laser-ablated in the cover plate 316 and arranged to communicate with the terminus when the cover plate is positioned over the column substrate.

Detailed Description Text (110):
The manifold 306 includes a plurality of ports that are configured to correspond with various apertures and inlets present in the cover plate 316 when the manifold is moved between positions relative to the column device 304. In one particular apparatus, the movable manifold 306 comprises a rotor that is butt-coupled to a stator (not shown) present on the external surface of the miniaturized column device 304, whereby the rotor is capable of moving about the stator between selected positions relative to the column device. When the column device is formed in a polyimide substrate, a ceramic rotor, pressed to the device using tensioned force (to form a liquid-tight seal), is capable of rotating between selected aperture positions on the device due to the friction characteristics of the two materials. Other suitable rotors can be formed in rigid materials such as glass and other non-conductive substrates.

Detailed Description Text (111):
Referring particularly to FIG. 14, the manifold 306 includes a first port 326, a second port 328, a third port 330 and a fourth port 332, each port being configured to accept an associated conduit means 334, 336, 338, and 340, respectively. The conduit means are in fluid communication with associated fluid containment means (not shown), such that a fluid sample, reagent or buffer can be communicated to the various ports in the manifold 306 for delivery into the column device 304. Referring now to FIGS. 14 and 15A, when the manifold 306 is in a first position, the first manifold port 326 is in fluid communication with the upstream terminus 308 of the separation channel 310. In this position, a suitable liquid medium, such as an equilibrating buffer or a flush solution, can be delivered into the separation

compartment (at the upstream terminus 308) from an associated containment means via the conduit means 334. Further, when the manifold is in the first position, the third manifold port 330 is in fluid communication with the upstream terminus of the makeup flow channel 320. Thus, a suitable liquid medium can be delivered into the makeup flow compartment (at the upstream terminus 322) from the same, or a different associated containment means, via the conduit means 338.

Detailed Description Text (112):
Referring now to FIGS. 14 and 15B, when the manifold 306 has been rotated counter-clockwise about the stator to a second position relative the column device 304, the fourth manifold port 332 is brought into fluid communication with the upstream terminus 308 of the separation channel 310. Accordingly, a volume or aliquot of liquid sample can be delivered into the separation compartment (at the upstream terminus 308) from an associated sample containment means via the conduit means 340. When the manifold is arranged in the second position, the first and third manifold ports 326 and 330 are moved out of fluid communication with the separation compartment and the makeup fluid compartment such that liquid medium is no longer delivered into those compartments via conduit means 334 and 338. Further, in the second position, the second manifold port 328 is aligned to be in fluid communication with the upstream terminus 322 of the makeup fluid channel 320, and a liquid reagent, or a heated makeup fluid can be delivered into the makeup flow compartment (at the upstream terminus 322) from an associated sample containment means via the conduit means 336.

Detailed Description Text (113):
Accordingly, a liquid phase separation can be readily carried out using the apparatus 302, wherein the manifold 306 allows switching between a stand-by mode when the manifold is in the first position, and a separation mode when the manifold is in the second position. Alternatively, the above-described two position manifold can be used to alternate between a sample run position, corresponding to the manifold being arranged in the first position, and a sample loading position, corresponding to the manifold being arranged in the second position. The manifold 306 is switched to the second position (e.g., the position depicted in FIG. 15B) to deliver a particular volume of sample into the separation compartment. Once the sample has been delivered, the manifold is rotated clockwise about the stator to return to the first position relative the column device (e.g., the position depicted in FIG. 15C) in order to conduct liquid phase separation of the sample.

Detailed Description Text (116):
A liquid phase separation apparatus may be provided having a movable manifold, wherein the manifold cooperates with an on-device volumetric sample compartment (e.g, a covered bypass channel in fluid communication with inlet and outlet means as described above), to enable the delivery of a sample plug of known volume from the sample compartment to the upstream terminus of a separation compartment. The manifold is detachably coupled to a miniaturized column device, and arranged in a first position such that external conduits disposed within two ports of the manifold enable dynamic fluid communication between the sample compartment (via the inlet and outlet means) and an associated sample containment means. A sample plug, having a volume corresponding to the dimensions of the volumetric sample compartment, is formed by the dynamic flow of sample through the compartment. By moving the manifold to a second position, different ports in the manifold are brought into fluid communication with the volumetric sample compartment inlet and outlet, whereby those ports allow the flow of an externally housed liquid medium through the sample compartment and into the separation compartment via associated conduits and/or lateral ports in the manifold. In this manner, the sample plug disposed within the volumetric sample compartment can be readily delivered to the separation compartment using known liquid injection techniques.

Detailed Description Text (117):
An apparatus may also be provided having a movable manifold that includes an internal volumetric sample compartment. Referring now to FIGS. 16 and 17, a liquid phase separation apparatus is generally indicated at 352. The apparatus includes a miniaturized column device 354, having a substrate portion 356 and a cover plate 358. A separation channel 360 is laser-ablated in a planar surface of the substrate portion 356. The separation channel has an upstream terminus 362 disposed in close proximity to three discrete laser-ablated microchannels, 364, 366, and 368, that are also formed in the substrate portion 356. The microchannel 364 has a first and second terminus, respectively indicated at 370 and 372. Likewise, the microchannel 366 has a first and second terminus, 374 and 376, and the microchannel 368 has a

first and second terminus 378 and 380.

Detailed Description Text (118):
A separation compartment is formed by arranging the cover plate 358 over the planar surface of the substrate portion 356. The cover plate includes a plurality of apertures that are arranged to provide fluid communication with the separation compartment and the microchannels 364, 366 and 368 when the cover plate is in place above the substrate. Specifically, laser-ablated apertures 382 and 390, are respectively in fluid communication with the first and second terminus, 370 and 372, of the microchannel 364 to provide a first flow path. Laser-ablated apertures 384 and 392 are respectively in fluid communication with the first and second terminus, 378 and 380, of the microchannel 368 to provide a second flow path. A third flow path is provided by apertures 388 and 394, that are respectively in fluid communication with the first and second terminus, 374 and 376, of the microchannel 366. An aperture, 386, is in fluid communication with the upstream terminus 362 of the separation channel 360.

Detailed Description Text (120):
In a first position relative to the column device 354, the manifold 396 is arranged such that the manifold port 398 is in fluid communication with the aperture 390, the first terminus 412 of the internal sample compartment is in fluid communication with the aperture 382, the second terminus 414 of the internal sample compartment is in fluid communication with the aperture 384, and the manifold port 400 is in fluid communication with the aperture 392. In this first position, the manifold 396 enables one continuous flow path to be established when the conduit means 404 is communicated with an associated containment means housing a sample. Particularly, the sample is delivered to the microchannel 364 via the conduit means and passed to the volumetric sample compartment 410, continuing through the microchannel 368, and exiting the apparatus via the conduit means 406. Thus, a sample plug is formed within the volumetric sample compartment by the dynamic passage of sample therethrough.

Detailed Description Text (121):
Once a sample plug has been formed in the sample compartment 410, the manifold can be moved to a second position relative to the column device 354 by rotating the manifold counter-clockwise about a pivot (not shown) to bring the manifold port 402 into fluid communication with the aperture 394. Further, the second terminus 414 of the internal sample compartment is brought into fluid communication with the aperture 388, and the first terminus 412 of the internal sample compartment is brought into fluid communication with the aperture 386. In this position, the sample plug can be readily flushed from the volumetric sample compartment and into the separation compartment by passing a liquid medium from an external containment means through the manifold via the conduit means 408, whereby the medium passes through the aperture 394 to flow through the microchannel 366, continuing through the sample compartment 410, and passing through the aperture 386 to the upstream terminus 362 of the separation channel 360.

Detailed Description Text (123):
The present invention combines miniaturized device technology described above combined with NMR detection in a single fabricated device wherein, using techniques described herein, a wide variety of microstructures may be formed, as will be appreciated by those working in the field of liquid phase analysis devices. The miniaturized device includes an NMR rf microcoil in series with the separation compartment at the point of detection. The microcoil can be fabricated directly into the separation device, as illustrated in FIG. 24A and as disclosed in the Example which follows. Alternatively, as shown in FIG. 24B, a microcoil-containing module can be manufactured separate from the separation device and inserted into the device prior to use to give a liquid-tight seal with zero dead volume.

Detailed Description Text (125):
Commonly used coil geometries include, but are not limited to, solenoid, Helmholtz, surface coil, birdcage coil, slotted-tube resonator, elliptical, back-to-back, and the like. Preferably, a coil geometry is used that provides signal-to-noise ratios of at least 3:1 and up to about 1000:1, preferably up to about 300:1, with good peak resolution, e.g. about 0.1 ppm, and minimal distortion of the main magnetic field.

Detailed Description Text (128):
One of skill in the art will recognize that any coil geometry can be used providing the sample and coil can be situated perpendicular the main magnetic field. Where

signal-to-noise is a concern, a series of coils with separate transmit and receive circuitry can be repeated along the length of the detection chamber, provided that the region of interest covered by the coils does not exceed the homogeneous volume of the main magnetic field. Furthermore, multiple receive-only coils can be used with a single transmit coil for signal-to-noise optimization in situations where a single coil with multiple turns might exceed resistance constraints.

Detailed Description Text (130):
FIGS. 24A and 24B illustrate a miniaturized device as illlustrated in FIG. 10 further comprising an integrated microcoil and a minaturized column device with a microcoil-containing module, respectively. The device, generally indicated at 500A and 500B, comprises a support body 502A and 502B having first and second component halves indicated at 504A, 504B and 506A, 506B, respectively. The first and second component halves 504A, 504B and 506A, 506B, each having substantially planar interior surfaces (not illustrated) into which microchannel has been microfabricated which, when the interior surfaces of the first and second planar halves are aligned in facing abutment with each other form elongate bore 508A, 508B. The elongate bore communicates with inlet port 510A, 510B and outlet port 512A, 512B, which enables the downstream passage of fluid from an external source through the elongate bore. In the embodiment illustrated in FIG. 24A, NMR detection compartment 514A around which is NMR rf microcoil 516A is situated downstream from inlet port 510A and in fluid communication with the elongate bore.

Detailed Description Text (131):
In the embodiment illustrated in FIG. 24B, NMR detection compartment 514B, around which is NMR rf microcoil 516B, are housed in module 518B. Elongate bore 508B terminates in upstream and downstream means 520B and 522B to form a liquid-tight, zero dead volume seal with complementary means 524B and 526B in module 518B.

Detailed Description Text (133):
The circuitry illustrated in FIG. 24A comprises means 534A for introducing an NMR signal through a tone/match circuit 536A into microcoil 516A. After passing through microcoil 516A, the signal is fed into preamplifier circuit 538A and to means 538A for receiving the coil output signal.

Detailed Description Text (134):
The circuitry illustrated in FIG. 24B comprises means 534B for introducing an NMR signal into microcoil 516B. Device 500B and module 518B include means 542B, 542B' and 544B, 544B' for establishing electrical communication therebetween. After passing through microcoil 516B, the signal is fed into preamplifier circuit 538B and to means 538B for receiving the coil output signal.

Detailed Description Text (135):
For signal detection of nanoliter volumes, the coil would have a diameter preferably about 50 .mu.m to about 100 .mu.m and a length of 1 mm. The coil may be silver or gold or any metal optimizing the conductive characteristics of the coil. The coil may be supercooled to improve signal-to-noise. The geometry of the coil is chosen to optimize the filling factor, i.e., the number of resonant nuclei per unit volume, while maintaining the stability and functionality of the planar device. Preferably, the separation chamber is of uniform diameter throughout, with a wall thickness of between about 5 .mu.m and about 10 .mu.m. For CE, a bore diameter of 75 .mu.m is preferred to avoid convective mixing from joule heating and head pressure. The volume of the sample chamber can range from less than about 10 nanoliters to 1000 nanoliters.

Detailed Description Text (136):
In addition to the NMR rf microcoil detector, other detection means may be interfaced with sample separation compartment, e.g., to serve as a sample detector and NMR trigger. For this purpose, an aperture is formed for communication with the elongate bore or sample processing compartment formed in the support body at a point upstream of the NMR microcoil detection compartment. A second aperture may be formed to communicate with the elongate bore or sample processing compartment downstream of the NMR microcoil detection compartment. The apertures serve as conduits for placing lightguide means, electrodes or other detection means in communication with the elongate bore or sample processing compartment to detect a sample passing therethrough. For example, first and second lightguide means (not shown) can be interfaced with first and second apertures to communicate with the sample processing compartment. Such lightguides can comprise optical fibers that are capable of sample illumination and light collection to enable near IR or UV-VIS optical detection of

separated analytes passing through the separation compartment. The detection of separated analytes prior to their entry into the NMR detection chamber may be used for NMR signal enhancement. For example, the flow rate of analyte can be adjusted to increase its concentration within the NMR detection chamber.

Detailed Description Text (137):
The device with rf microcoil and associated fluid inputs and outputs is intended to be placed at the isocenter of the magnetic field of an NMR spectrometer. Various interfacing arrangements can be envisaged.

Detailed Description Text (138):
In one arrangement, as shown in FIG. 25, the separation device shown generally at 500C having an integrated rf microcoil 516C is hyphenated with a miniature (tabletop) NMR magnet shown at 550. The miniature NMR magnet includes tune-and-match circuitry 552, transmit/receive electronics 554, and central computer 556 for acquisition control, data storage and signal processing. Associated electronics 558 for frequency synthesis, amplifiers, waveform generators, attenuators and pulse sequence generators for signal acquisition are controlled by the computer. Thus, in this arrangement, the tune-and-match circuitry 552 as well as the preamplifiers are separate from the miniaturized device and part of the standard configuration of the NMR magnet. Alternatively, device 500C can be fabricated as illustrated in FIG. 24A to include tune-and-match circuitry as well as preamplifiers, and the tune/match/preamplifier circuitry on the miniature NMR magnet can be bypassed.

Detailed Description Text (139):
In a second arrangement, the miniaturized separation device 500A, as illustrated in FIG. 24A, with rf microcoil 516A is hyphenated into a micromagnet NMR system. Recent technological advances in high temperature superconductors, refrigeration and pulsed field magnets suggest the feasibility of much smaller "table-top" magnets. These micro-magnets may be configured to accept the device with rf microcoil having on-board preamplifiers and/or tune and match circuitry in a manner analogous to a CD player accepting a CD disk. This micro-magnet configuration could be used as well to examine multiple devices in series, e.g., fed in on a roll following sample preparation in a "batch" mode, thereby allowing routine automated detection of multiple samples.

Detailed Description Text (140):
The advantages of having a miniaturized separation device integrated with an NMR rf microcoil include: (1) a faster time-to-result with on-line NMR analysis; (2) avoidance of sample dilution from remote sample injection; (3) sample handling capability to provide an NMR-ready sample at the point of detection; (4) increased sensitivity of NMR detection; and (5) low cost-high volume manufacture of consumable devices that are small enough to be accommodated in any high field NMR system.

Detailed Description Text (145):
FIG. 26A and FIG. 26B illustrate top and side view of planar column device 600 with integrated NMR rf microcoil 602 includes sample and buffer inlet ports 604, 606, 608, 610, in switchable fluid communication via manifold 612 with solid phase extraction chamber 614 by inlet port 614. Extraction chamber 614 is filled with solid phase extraction material 618. The design of the device is based on the multifold geometry disclosed in commonly assigned U.S. Pat. No. 5,658,413 to Kaltenbach et al. for "Miniaturized Planar Columns in Novel Support Media for Liquid Phase Analysis."

Detailed Description Text (146):
Extraction chamber 614 is connected to an outlet channel 620 which, in turn, is connected with rotor 622, e.g., a port/valve 624 and conduit 626 assembly, for selectably directing the flow from the outlet channel to waste outlet 628 or to valve/port 630 that leads through the device thus allowing further processing or analysis of the sample. For example, valve 624 would direct voiding of unwanted fluid from solid phase extraction chamber 614 or through-flow to an NMR detection chamber 632. Fluid that is to be flushed from the system/device to waste, for example, would flow from solid-phase extraction chamber 614 through channel 620 to valve/port 624 and into conduit 626 to waste outlet 628, by which fluid can be voided to the exterior of the device. Closing of waste outlet 628, and opening of valve/port 630 allows fluid to continue through channel 634 and, thereafter, through NMR detection chamber 632. Fluid exits detection chamber 632 through port 636, from which the effluent may be collected or discarded.

Detailed Description Text (150):
As an example of the function of such a device, as illustrated in FIG. 26D, the simultaneous measurement of drug metabolites is provided. Manifold 612 is turned so that sample line 604 is in fluid communication with inlet port 616. One milliliter of a urine sample prepared as described in Wilson et al., supra is pumped through the chamber 614 packed with film 618 having the chemical properties of a reverse phase medium. Second rotor 622 is a one-port, two-position valve allowing flow of solute directly through the device through valve/port 624 into conduit 626 and through port 630, or to be flushed out of the system as effluent through port 628. Rotor 622 is positioned so that valve/port 624 is connected to waste line 628 during the sample flushing step. Rotor 612 is then turned so that the buffer line 606 is in fluid communication with inlet port 616. The excess urine is washed from the system through waste line 628. The solutes of interest are adsorbed onto packed bed 618 of chamber 614.

Detailed Description Text (151):
The following step are the sample elution step. Solutes of increasing hydrophobic character elute according to increasing percentage of organic modifier in the release solution. Rotor 622 is positioned so that valves/ports 624 and 630 are in fluid communication with inlet port 616 and outlet port 636. In five steps ranging from 20% methanol to 100% methanol using 20% increasing increments of methanol, solutes are eluted from the packed bed medium 618 in chamber 614 to the NMR detection chamber 632. At each elution step, the NMR spectrum of the eluted sample is obtained.

Detailed Description Text (152):
After all five step elutions have been completed, packed bed medium 618 is re-equilibrated to the original aqueous buffer conditions by setting rotor 622 so that port 624 is in fluid communication with waste line 628. After sufficient bed volumes of buffer have been flushed through the system, the procedure described above for sample introduction and adsorption, elution and measurement are repeated using elution solutions containing methanol to which a chemical shift reagent has been added.

Detailed Description Text (155):
Plug flow of the released solute arrived at the NMR chamber via the one-port, two-position rotor 622. Sample detection can either be through stopped flow or flow-through mode. Stopped flow involves acquisition of the NMR signal while the sample plug resides in the homogeneous volume of the detector coil. The region of signal is roughly defined as the volume of the sample enclosed by the radio-frequency coil 602. There is little signal detection from the edges of the coil. With the stopped flow method, signal averaging continues until enough signal is obtained from the sample, minimally 3:1 signal-to-noise. With the flow-through method, signal will be obtained from sample from the time it enters the coil 602, until no more sample is released from the solid phase extraction chamber 614. Some contamination of signal may arise when acquisition occurs before sample arrives in the homogeneous volume of the coil and after it leaves the homogeneous volume of the coil. Volume localized spectroscopy has been used to determine how much of a sample is contributing to a signal within the homogeneous volume. Spectra can be summed and weighted depending on the ratio of sample to unwanted signal.

CLAIMS:

1. A miniaturized total analysis system for liquid phase sample preparation and detection comprising:

a microfabricated support body having first and second substantially planar opposing surfaces wherein the support body has a microchannel microfabricated in the first planar surface;

a cover plate arranged over the first planar surface, wherein the cover plate in combination with the first microchannel forms a sample processing compartment;

an inlet port and an outlet port communicating with the sample processing compartment, wherein the inlet and outlet ports enable downstream passage of fluid from an external source through the sample processing compartment; and

downstream from the sample processing compartment and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil, wherein

the NMR detection compartment and the NMR rf microcoil are housed within the support body.

2. The miniaturized total analysis system of claim 1, wherein the NMR detection compartment and the NMR rf microcoil comprise microstructures fabricated in the support body.

3. The miniaturized total analysis system of claim 1, wherein the NMR detection compartment and the NMR rf microcoil comprise a modular structure removably insertable into the support body.

4. The miniaturized total analysis system of claim 1, wherein the NMR rf microcoil is selected from the group consisting of solenoid coils, Helmholtz coils, surface coils and birdcage coils.

6. The miniaturized total analysis system of claim 4, wherein the NMR rf microcoil is a receive-only coil.

7. The miniaturized total analysis system of claim 6, wherein the NMR rf microcoil is comprised of multiple receive-only coils.

17. A miniaturized total analysis system for liquid phase sample preparation and detection, comprising:

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces;

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

an inlet port and an outlet port communicating with the elongate bore, the ports enabling the downstream passage of fluid from an external source through the elongate bore; and

downstream from the elongate bore and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil, wherein the NMR detection compartment and the NMR rf microcoil are housed within the support body.

18. The miniaturized total analysis system of claim 17, wherein the NMR detection compartment and the NMR rf microcoil comprise microstructures fabricated in the support body.

19. The miniaturized total analysis system of claim 17, wherein the NMR detection compartment and the NMR rf microcoil comprise a modular structure removably insertable into the support body.

20. The miniaturized total analysis system of claim 17, wherein the NMR rf microcoil is selected from the group consisting of solenoid coils, Helmholtz coils, surface coils and birdcage coils.

22. The miniaturized total analysis system of claim 20, wherein the NMR rf microcoil is a receive-only coil.

23. The miniaturized total analysis system of claim 22, wherein the NMR rf microcoil is comprised of multiple receive-only coils.

33. A miniaturized total analysis system for liquid phase sample preparation and detection, comprising:

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces;

a first microchannel microfabricated in the interior surface of the first support

body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

a sample processing compartment comprising an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

an inlet port and an outlet port communicating with the sample processing compartment, the ports enabling the downstream passage of fluid from an external source through the sample processing compartment; and

downstream from the sample processing compartment and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil, wherein the NMR detectioncompartment and the NMR rf microcoil are housed within the support body.

34. The miniaturized total analysis system of claim 33, wherein the NMR detection compartment and the NMR rf microcoil comprise microstructures fabricated in the support body.

35. The miniaturized total analysis system of claim 33, wherein the NMR detection compartment and the NMR rf microcoil comprise a modular structure removably insertable into the support body.

36. The miniaturized total analysis system of claim 33, wherein the NMR rf microcoil is selected from the group consisting of solenoid coils, Helmholtz coils, surface coils and birdcage coils.

38. The miniaturized total analysis system of claim 36, wherein the NMR rf microcoil is a receive-only coil.

39. The miniaturized total analysis system of claim 38, wherein the NMR rf microcoil is comprised of multiple receive-only coils.

49. An integrated device for sample preparation and NMR detection, comprising:

(a) a miniaturized total analysis system for liquid phase sample preparation and detection, comprising

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces,

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other,

an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore,

an inlet port and an outlet port communicating with the elongate bore, the ports enabling the downstream passage of fluid from an external source through the elongated bore

downstream from the elongate bore and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil, wherein the NMR detection compartment and the NMR rf microcoil are housed within the support body; and

(b) a magnet configured to accept the miniaturized total analysis system, wherein the device is capable of generating an NMR spectrum.

50. The integrated device of claim 49, wherein the NMR detection compartment and the NMR rf microcoil comprise microstructures fabricated in the support body.

51. The integrated device of claim 49, wherein the NMR detection compartment and the NMR rf microcoil comprise a modular structure removably insertable into the support body.

52. The integrated device of claim 49, wherein the NMR rf microcoil is selected from the group consisting of solenoid coils, Helmholtz coils, surface coils and birdcage coils.

54. The integrated device of claim 52, wherein the NMR rf microcoil is a receive-only coil.

55. The integrated device of claim 54, wherein the NMR rf microcoil is comprised of multiple receive-only coils.

65. An integrated device for sample preparation and NMR detection, comprising:

(a) a miniaturized total analysis system for liquid phase sample preparation and detection, comprising

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces,

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other,

a sample processing compartment comprising an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore,

an inlet port and an outlet port communicating with the sample processing compartment, the ports enabling the downstream passage of fluid from an external source through the sample processing compartment, and

downstream from the sample processing compartment and in fluid communication therewith, an NMR detection compartment around which is an NMR rf microcoil, wherein the NMR detection compartment and the NMR rf microcoil arc housed within the support body; and

(b) a magnet configured to accept the miniaturized total analysis system, wherein the device is capable of generating an NMR spectrum.

66. The integrated device of claim 65, wherein the NMR detection compartment and the NMR rf microcoil comprise microstructures fabricated in the support body.

67. The integrated device of claim 65, wherein the NMR detection compartment and the NMR rf microcoil comprise a modular structure removably insertable into the support body.

68. The integrated device of claim 65, wherein the NMR rf microcoil is selected from the group consisting of solenoid coils, Helmholtz coils, surface coils and birdcage coils.

70. The integrated device of claim 68, wherein the NMR rf microcoil is a receive-only coil.

71. The integrated device of claim 70, wherein the NMR rf microcoil is comprised of multiple receive-only coils.

81. The miniaturized total analysis system of claim 1, wherein the support body is comprised of a material other than silicon or silicon dioxide and the miniaturized total analysis system provides a signal-to-noise ratio of at least 3:1.

82. The miniaturized total analysis system of claim 17, wherein the support body is comprised of a material other than silicon or silicon dioxide and the miniaturized total analysis system provides a signal-to-noise ratio of at least 3:1.

83. The miniaturized total analysis system of claim 33 wherein the support body is comprised of a material other than silicon or silicon dioxide and the miniaturized total analysis system provides a signal-to-noise ratio of at least 3:1.

84. The integrated device of claim 49, wherein the support body is comprised of a material other than silicon or silicon dioxide and the integrated device provides a signal-to-noise ratio of at least 3:1.

85. The integrated device of claim 65, wherein the support body is comprised of a material other than silicon or silicon dioxide and the integrated device provides a signal-to-noise ratio of at least 3:1.

86. A miniaturized total analysis system for liquid phase sample preparation and detection comprising:

a microfabricated support body having first and second substantially planar opposing surfaces wherein the support body has a microchannel microfabricated in the first planar surface;

a cover plate arranged over the first planar surface, wherein the cover plate in combination with the first microchannel forms a sample processing compartment;

an inlet port and an outlet port communicating with the sample processing compartment, wherein the inlet and outlet ports enable downstream passage of fluid from an external source through the sample processing compartment; and

downstream from the sample processing compartment, a module comprising an NMR detection compartment and an NMR rf microcoil, the module being insertable into the support body such that the NMR detection compartment is in fluid communication with the sample processing compartment.

87. A miniaturized total analysis system for liquid phase sample preparation and detection, comprising:

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces;

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

an inlet port and an outlet port communicating with the elongate bore, the ports enabling the downstream passage of fluid from an external source through the elongate bore; and

downstream from the elongate bore, a module comprising an NMR detection compartment and an NMR rf microcoil, the module being insertable into the support body such that the NMR detection compartment is in fluid communication with the elongate bore.

88. A miniaturized total analysis system for liquid phase sample preparation and detection, comprising;

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces;

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

a sample processing compartment comprising an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

an inlet port and an outlet port communicating with the sample processing compartment, the ports enabling the downstream passage of fluid from an external source through the sample processing compartment; and

downstream from the sample processing compartment, a module comprising an NMR detection compartment and an NMR rf microcoil, the module being insertable into the support body such that the NMR detection compartment is in fluid communication with the sample processing compartment.

89. An integrated device for sample preparation and NMR detection, comprising:

(a) a miniaturized total analysis system for liquid phase sample preparation and detection, comprising:

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces;

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

an inlet port and an outlet port communicating with the elongate bore, the ports enabling the downstream passage of fluid from an external source through the elongate bore; and

downstream from the elongate bore, a module comprising an NMR detection compartment and an NMR rf microcoil, the module being insertable into the support body such that the NMR detection compartment is in fluid communication with the elongate bore; and

(b) a magnet configured to accept the miniaturized total analysis system, wherein the device is capable of generating an NMR spectrum.

90. An integrated device for sample preparation and NMR detection, comprising:

(a) a miniaturized total analysis system for liquid phase sample preparation and detection, comprising:

a microfabricated support body having first and second component halves each having substantially planar opposing interior and exterior surfaces;

a first microchannel microfabricated in the interior surface of the first support body half and a second microchannel microfabricated in the interior surface of the second support body half, wherein each of the microchannels is so arranged as to provide the mirror image of the other;

a sample processing compartment comprising an elongate bore formed by aligning the interior surfaces of the support body halves in facing abutment with each other whereby the microchannels define the elongate bore;

an inlet port and an outlet port communicating with the sample processing compartment, the ports enabling the downstream passage of fluid from an external source through the sample processing compartment; and

downstream from the sample processing compartment, a module comprising an NMR detection compartment and an NMR rf microcoil, the module being insertable into the support body such that the NMR detection compartment is in fluid communication with the sample processing compartment; and

(b) a magnet configured to accept the miniaturized total analysis system, wherein the device is capable of generating an NMR spectrum.